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The stressed brain

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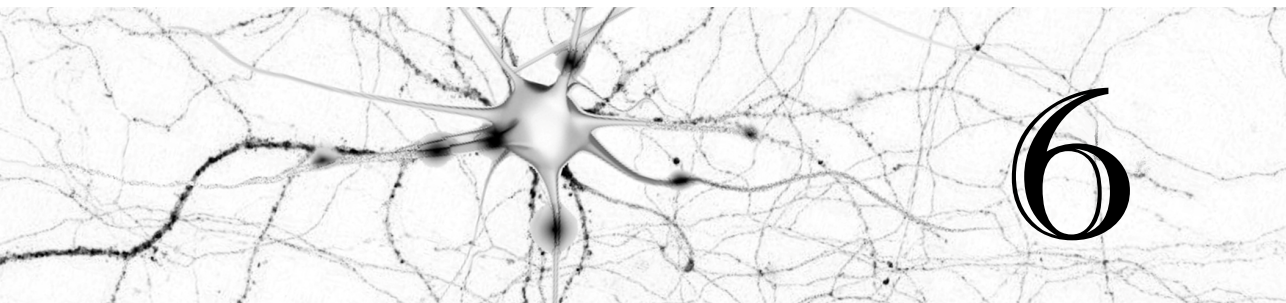
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THE CHOLINERGIC SYSTEM AND DEPRESSION

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ABSTRACT

Major depressive disorder is a severe psychiatric condition which forms a substantial burden to patients and society. Despite continuous efforts to unravel its etiology and pathophysiology, many questions remain. The majority of neurobiological research and classical pharmacotherapy regimens have approached this illness as the consequence of a failing monoaminergic neurotransmitter system. In the last decades, involvement of adult hippocampal neurogenesis in the pathogenesis and treatment of depressive disorder has gained an enormous interest. Numerous neurobiological systems and circuits thus appear to underlie this complex multifactorial disease. One of them is the cholinergic system, which plays a major role in the regulation of various CNS functions, such as arousal, attention, cognition and memory. Cognitive impairments are often observed in depression, next to low mood, anhedonia and other clinical symptoms. Cholinergic dysfunctions may account for the development of cognitive symptoms during the course of depression. Changes in hippocampal neurogenesis, often associated with chronic stress in animal models, may be in part mediated by cholinergic dysfunction, which in turn could underlie the cognitive disturbances observed in depression. Here, we discuss the involvement of the cholinergic system in depressive disorder, with particular focus on its role in associated cognitive impairment. Since such deficits are often modified by cholinergic drugs, application of these neuropharmacological findings may provide a new therapeutic niche while yielding valuable insight into the pathophysiology of this complex illness.

INTRODUCTION

Major depressive disorder is a multidimensional syndrome which involves disruption of mood, cognition and other processes, including sleep, appetite and libido (Nestler et al., 2002a). Depression has been described since antiquity but it is still conceptualized as a common and complex disease of unknown etiology. Research attempts to elucidate the mechanisms responsible for development and treatment of depression have yielded valuable insight, but its puzzling nature persists. For half a century, the majority of neurobiological research and classical pharmacotherapy regimens have explained this illness with the monoamine hypothesis of depression, which proposes that low levels of brain monoamines, such as serotonin, noradrenaline and dopamine, are responsible for the development of depressive symptoms. In contrast, many currently used antidepressant drugs, such as selective serotonin reuptake inhibitors (SSRI), noradrenaline reuptake inhibitors (NRI), serotonin and noradrenaline reuptake inhibitors (SNRI), tricyclics and monoamine oxidase inhibitors (MAOI) potentiate the brain's monoaminergic system and elevate the monoamine levels (Wong and Licinio, 2001). Despite their acute effects on the monoaminergic system, however, the mood-alleviating properties of all these medications take at least several weeks to become manifest (Berton and Nestler, 2006). Therefore, although considerably advancing the way depression was viewed and treated, the monoamine hypothesis has failed to fully explain the nature of this disorder (Maes, 2009). The discovery of adult hippocampal neurogenesis seemed again to revolutionize the understanding of the neurobiological mechanisms governing depression and antidepressant therapies as it proved to be affected by stress, yet restored by antidepressants (Krishnan and Nestler, 2008). Despite contradictions in literature, the possibility that hippocampal neurogenesis may be oppositely regulated by depression and antidepressants, gained enormous interest among researchers and great enthusiasm among clinicians. Nevertheless, although initially promising, this phenomenon has lost some of its appeal due to difficulties providing functional mechanism for the etiology of depression. Not surprisingly, failure of one neurobiological system is not sufficient to explain the nature of such a complex disorder as depression. Numerous brain systems and neuronal networks act in concert to maintain normal functioning; likewise, in depression many of them may get dysregulated. One of those is the cholinergic system, responsible for a number of CNS functions, including arousal, attention, learning and memory.

Cognitive impairments are often observed in depression, in addition to mood disturbances and other motoric, autonomic, endocrine and sleep-wake abnormalities. This spectrum of symptoms is thought to arise from the complex interaction between

multiple genetic and environmental factors (Manji et al., 2001). It has been hypothesized that different neurotransmitter-mediated dysfunctions may subserve specific symptom domains. Depression-associated anxiety is thought to arise from abnormal serotonergic function, whereas loss of pleasure, interest and energy may be due to dopaminergic and noradrenergic deficits (Nutt et al., 2007). Cholinergic dysfunctions may account for the development of cognitive symptoms associated with depression, especially when the disease is long-lasting and treatment resistant. Moreover, changes in hippocampal neurogenesis may be in part mediated by the cholinergic system and may also relate to the cognitive disturbances diagnosed in depression.

Here, we review the literature regarding involvement of the cholinergic system in the pathophysiology of depressive disorder. First, the history of the cholinergic hypothesis of depression is summarized. Then, the contribution of cholinergic changes to the development of mood and cognitive impairments associated with depression is discussed. In view of this, we outline a potential link between the cholinergic system, hippocampal neurogenesis and cognitive dysfunction in depression. In addition to the hippocampal changes mediated by cholinergic transmission, we briefly discuss the alterations in other brain areas, implicated in depression and innervated by cholinergic neurons, i.e. the prefrontal cortex, amygdala, and the suprachiasmatic nucleus (SCN). On a final note, we emphasize that depression-associated symptoms depend on complex changes in a variety of neurobiological systems and multiple brain areas. Thus, future research would benefit from an integrated view on depression, attempting to unravel these multifactorial interactions in search of novel therapeutic targets.

THE CHOLINERGIC HYPOTHESIS OF DEPRESSION

Implication of the cholinergic system in the etiology of major depression, although not as widely accepted as the monoamine hypothesis, was postulated several decades ago. It was suggested that central cholinergic activation caused depressant inhibitory effects, while anticholinergic drugs or adrenergic stimulation induced behavioral activation and arousal (Carlton, 1963; Vaillant, 1967; Domino and Olds, 1968). Based on these observations, Janowsky and co-workers postulated the cholinergic-adrenergic imbalance hypothesis of depression and mania (Janowsky et al., 1972). Central cholinergic factors were suggested to play a role in the etiology of affective disorders, and depression was proposed to be a disease of cholinergic dominance. This hypothesis originated from reports showing that cholinesterase

inhibitors induced depressive symptoms, presumably through increased central acetylcholine levels. The first study of this kind involved administration of the irreversible cholinesterase inhibitor diisopropylfluorophosphonate (DFP), which was found to induce depression-like symptoms in normal subjects and decrease mania-like symptoms in manic patients (Rowntree et al., 1950). This was supported by the case reports of individuals poisoned with cholinesterase inhibitor insecticides, who developed depression symptoms and peripheral parasympathetic toxicity (Gershon and Shaw, 1961). Another irreversible cholinesterase inhibitor, EA-1701, was also noted to cause depressed mood and lethargy in healthy volunteers (Bowers et al., 1964). Later, the reversible inhibitor of cholinesterase, physostigmine, was shown to induce depressive symptoms and exacerbate mood disorders (Janowsky et al., 1973; Janowsky et al., 1974; Davis et al., 1976). Choline treatment was also associated with depressive symptoms, but only sporadically (Tamminga et al., 1976). Additional evidence for a cholinergic mechanism in depression came from the observation that the monoamine depletor reserpine, a drug which induced mood depressing effects, had central cholinomimetic properties (Janowsky et al., 1972; Davis et al., 1978). Cholinergic hypersensitivity was thus considered essential in depression with evidence of anticholinesterases and cholinomimetics producing acute syndromes characterized by dysphoria, psychomotor retardation and energy loss (Dilsaver, 1986). Despite their seemingly acute depressiogenic and antimanic properties, however, it is unclear whether these were illustrative of specific depression symptomology or a non-specific response of behavioral inhibition, secondary to cholinergic manipulation (Leong and Brown, 1987). Nevertheless, given these clinical observations, anticholinergic drugs have been investigated as potential treatments for depression, but studies have not reported consistent antidepressant effects (Goldman and Erickson, 1983; Shytle et al., 2002; Howland, 2009). In fact, the agonists of cholinergic nicotinic receptors have been associated with antidepressant properties, arguing against the cholinergic dominance hypothesis of depression (Ferguson et al., 2000; Gatto et al., 2004).

Neuroimaging studies have reported an increased concentration of the acetylcholine precursor, choline, in the brains of patients suffering from mood disorders and its reversal after recovery from depression (Charles et al., 1994; Steingard et al., 2000). However, postmortem brain analysis yielded no consistent results on the involvement of acetylcholine receptors in depression. Although a higher number of muscarinic acetylcholine receptor binding sites was reported in the frontal cortex of suicide victims (Meyerson et al., 1982), subsequent studies did not replicate this finding (Kaufmann et al., 1984; Stanley, 1984; Zavitsanou et al., 2004) or even opposed it (Gibbons et al., 2009). Cholinergic hypersensitivity was linked to a

personality trait predisposing to depression, such as stress sensitivity, rather than to depression itself (Fritze et al., 1995).

Importance of the cholinergic hypothesis of depression diminished over time, due to insufficient evidence linking it to the etiology of major depression. Even in the 1980s when this hypothesis was prominent, it was recognized that cholinergic pathology is unlikely to explain all the nuances of depression (Dilsaver, 1986). Nevertheless, recognizing the role of the cholinergic system in depression may shed light upon mechanisms involved in certain aspects of this disease. Therefore, the following text of this review will focus on cholinergic changes that may develop during the course of depression, and may thus account for specific clinical symptoms associated with this disorder.

ALTERED CHOLINERGIC FUNCTION IN DEPRESSION: INVOLVEMENT IN COGNITIVE RATHER THAN AFFECTIVE SYMPTOMS?

Low mood is the most prominent clinical symptom of major depressive disorder. Also, depression is often accompanied by significant impairments in neurocognitive functioning that may be independent of mood (Austin et al., 2001; Porter et al., 2003; Clark et al., 2009). Cognitive symptoms of depression, such as poor attention and concentration as well as impaired memory and information processing, point to deficits in cholinergic function. Acetylcholine is largely responsible for regulating these cognitive processes (Deutsch, 1971). Cholinergic projections from the basal forebrain system modulate the function of numerous brain areas implicated in depression, and the optimal range of cholinergic tone is vital for optimal behavioral and brain function (Roland et al., 2008). It is thus feasible that an imbalance of multiple neurobiological systems underlying depression results in cholinergic dysfunction which, in turn, causes further disruption (see figure 6.1).

Neuropharmacological evidence

Evidence regarding altered cholinergic function in depression mainly comes from drug studies targeting nicotinic or muscarinic cholinergic receptors. These two types of cholinergic receptors are widely expressed in the brain and often co-expressed within neurons (Schroder et al., 1991; van der Zee et al., 1991). Their action is suggested to contribute to both mood and cognitive symptoms of depression although

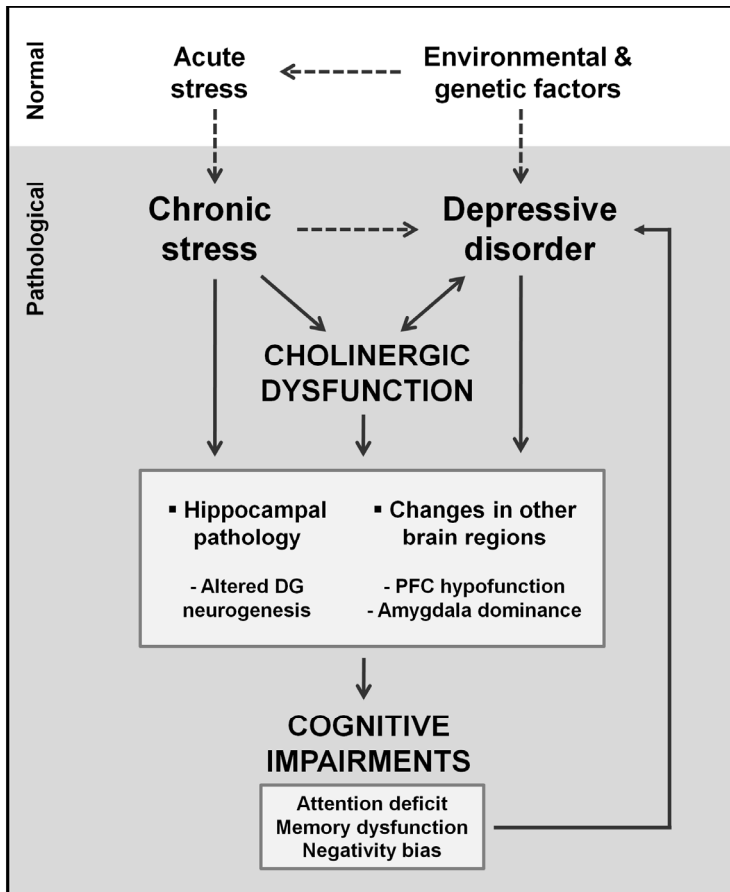


Figure 6.1 Depressive disorder is thought to arise from the complex interaction of multiple genetic and environmental factors. These factors may also lead to higher susceptibility to stress. Whereas the acute stress response is adaptive, prolonged stress may predispose to depression. Both chronic stress and depression are associated with cholinergic dysfunctions as well as with structural and functional alterations in multiple brain areas. Changes in the hippocampus, PFC and amygdala, observed in chronically stressed animals and/or depressed subjects, may partly arise from the cholinergic dysfunction. Altogether, these neurobiological alterations account for development of the cognitive symptoms of depression, such as attention deficit, memory impairment and negativity bias. Thus, cholinergic dysfunction may in part underlie depression-associated cognitive impairments, that in turn can precipitate the course of this illness. On the other hand, cholinergic dysfunction may also predispose to depression, via dysregulation of numerous neurobiological systems and circuits involved in the pathophysiology of this complex disorder.

Dashed arrows represent predisposing factors to depression. Solid arrows indicate the consequences that arise from pathological states of chronic stress and depression, causing further disruptions, that in turn may predispose and/or precipitate depressive disorder.

DG – dentate gyrus; PFC – prefrontal cortex.

the latter seem to be more plausible given the functional role of acetylcholine in the brain's cognitive processes. Nevertheless, nicotine has been shown to alleviate symptoms of depression in non-smoking depressed patients (Salin-Pascual et al., 1995). On the other hand, nicotine withdrawal can exacerbate depressive symptoms (Laje et al., 2001). Nicotine dependence is strongly correlated to mood disorders, e. g. smoking behavior relates to the genetic susceptibility to depression (Kendler et al., 1993; Lerman et al., 1998). Interestingly, schizophrenic subjects, also known to have a very high rate of smoking, may be using nicotine to self-medicate their cognitive impairments associated with schizophrenia (George et al., 2002; Sacco et al., 2005). The precise changes in cholinergic signaling through nicotinic receptors in depression are not known. Furthermore, the literature is confounded by studies reporting that both nicotine receptor agonists and antagonists may display antidepressant properties (Ferguson et al., 2000; Shytle et al., 2002; Gatto et al., 2004; Lippiello et al., 2008). However, their effects on cognitive functions seem to be diverse; whereas nicotinic agonists can improve attention, learning and memory, nicotinic antagonists can impair these processes (Levin and Simon, 1998; Hasselmo, 2006; McKay et al., 2007). Although both activation and desensitization of nicotinic acetylcholine receptors have been suggested to contribute to behaviors related to nicotine addiction and mood (Picciotto et al., 2008), their distinct role in depression remains unclear.

Similarly, there is little research providing direct evidence for a role of muscarinic receptors in the pathophysiology of major depressive disorder. Yet, pharmacological studies continue to recognize a potential for reducing depression-associated symptoms via modulation of the muscarinic system (Scarr, 2009). Cholinergic muscarinic agonists are shown to facilitate learning and memory, whereas antagonists are associated with deficits in these processes (Jerusalinsky et al., 1997; Power et al., 2003; Hasselmo, 2006). M1 metabotropic muscarinic receptors represent a viable target for amelioration of affective disorder-associated cognitive deficits, given their role in cognition (Scarr, 2009). M2 receptors were suggested to be involved in major depressive disorder by single-nucleotide polymorphism (SNP) association studies (Comings et al., 2002; Wang et al., 2004). This notion was further supported by a recent postmortem study, reporting decreased binding of M2 and/or M4 muscarinic receptors in the dorsolateral prefrontal cortex of depressed subjects (Gibbons et al., 2009).

Loss of cholinergic terminals results in memory deficits, confirming the above described neuropharmacological findings on cholinergic transmission and cognition (Jerusalinsky et al., 1997). Given the highly interactive nature of central nicotinic and muscarinic systems and their receptor co-localization, it is likely that

depression-induced changes in one subset of the cholinergic system modulate the other one too (Schroder et al., 1991; van der Zee et al., 1991; Lucas-Meunier et al., 2003). At present it is difficult to attribute distinct involvement of these two cholinergic receptor systems in the pathophysiology of depressive disorder, and the extent of this complexity goes beyond the scope of this review. As such, we will not elaborate upon specific effects achieved through the cholinergic receptor subtypes, but focus instead on the greater framework of cholinergic changes associated with mood disorders and their treatment.

It appears that some classical antidepressants also partially target cholinergic neurotransmission. The SSRI, citalopram, has been shown to reverse memory impairment by enhancing acetylcholine release in the hippocampus of laboratory animals (Egashira et al., 2006). It has also been reported to improve psychotic symptoms and behavioral disturbances in patients with dementia (Pollock et al., 2002) and facilitate memory consolidation in healthy volunteers (Harmer et al., 2002). Citalopram may thus possibly improve memory impairment in depressed patients by enhancing acetylcholine release (Egashira et al., 2006). The mood stabilizer, lithium, has also been shown to upregulate hippocampal cholinergic muscarinic receptors (Marinho et al., 1998), further emphasizing a role for the cholinergic system in the pathology of depression.

Cholinergic changes in depression and stress: contribution to cognitive dysfunction

Altered acetylcholine release in depression has been hypothesized but not clearly proven. Changes in central acetylcholine turnover have been reported in response to prolonged stress, a major predisposing risk factor for developing depression (Finkelstein et al., 1985; Gilad, 1987). Whereas an acute stress response is adaptive, chronic stress, especially when it is unpredictable and uncontrollable, may increase brain vulnerability to neuropathology (McEwen, 2004; de Kloet et al., 2005; Dagyte et al., 2009). Stress is known to alter the functioning of the cholinergic system (Gold, 2003; Srikumar et al., 2006). The stress response induces acetylcholine release in the forebrain and activates the septohippocampal pathway (Gilad, 1987). This mediates physiological and emotional responses, in part through acetylcholine action on the HPA-axis (Newman et al., 2001). While acute stressors increase acetylcholine release in the hippocampus (Mark et al., 1996; Dong et al., 2004), the effects of chronic stress are less clear (Mizoguchi et al., 2001; Srikumar et al., 2006), but may involve a gradual decline of cholinergic function. Chronic stress has been reported to decrease acetylcholinesterase (AChE) activity in the hippocampus of laboratory animals (Das

et al., 2000; Sunanda et al., 2000). Subsequently, such decrease in AChE activity was associated with learning and memory deficits after exposure to chronic stress (Srikumar et al., 2006). Cholinergic dysfunctions have also been reported in rats subjected to chronic unpredictable stress or corticosterone treatment, where a decrease in AChE-stained neurons in the medial septum was observed (Tizabi et al., 1989; Douma et al., 1999). Such stress-induced malfunctioning of the cholinergic system may in turn impair learning and memory processes (Gold, 2003; Srikumar et al., 2006). Preclinical studies using *in vivo* microdialysis techniques have shown that increased and decreased acetylcholine levels correlate with increased and decreased memory performance, respectively (Ragozzino et al., 1994; Ragozzino et al., 1996). In line with this, pharmacological augmentation of septohippocampal cholinergic activity enhances learning and memory performance in cognitively impaired animals (Roland et al., 2008).

There is a wealth of evidence indicating that stress, especially when severe and prolonged, can precipitate affective disorders and impair learning and memory (McEwen, 2000a, McEwen, 2000b). Chronic stress in laboratory animals has been associated with deficits in several learning and memory tasks, e.g. radial arm maze and Y-maze (Luine et al., 1994; Conrad et al., 1996; Srikumar et al., 2006). The hippocampal formation, governing these learning paradigms and densely innervated by cholinergic neurons (Gaykema et al., 1990; Woolf, 1991), is highly impacted by stress. Exposure to chronic stress or glucocorticoids has been demonstrated to affect the hippocampal neurons, causing a dendritic atrophy of CA3 pyramidal neurons, alteration in the density of dendritic spines and excrescences, and neuronal cell loss (Woolley et al., 1990; Sapolsky, 1993). Among the multiple neurochemical changes that occur in response to stress, excessive glutamatergic neurotransmission is thought to play a major role in stress-induced hippocampal neurotoxicity. Several studies have reported that exposure to stress increased the release of glutamate in the hippocampus and other brain regions, such as the prefrontal cortex and the basal ganglia (Watanabe et al., 1992; Moghaddam, 1993; Moghaddam et al., 1994). As such, excessive glutamate release is also implicated in neurodegeneration (Lee et al., 2002a). As the glutamatergic and cholinergic systems act in concert, changes in the former may synergically affect the latter, causing perturbations in learning, memory and other cognitive processes (Riederer and Hoyer, 2006).

Relationship between the cholinergic system and hippocampal neurogenesis: implication in depression

Several lines of evidence support the enhanced neurodegeneration and decreased neurogenesis hypothesis of depression (Maes, 2009). Structural brain changes have been reported in depressed patients, involving volumetric changes in hippocampus, amygdala, prefrontal cortex, anterior cingulate cortex and basal ganglia (Sheline, 2003; Campbell and MacQueen, 2006). Moreover, postmortem studies have revealed neuronal and glial cell modifications in the hippocampus in major depression (Stockmeier et al., 2004). The hippocampus serves as an integrator of input from various brain regions related to mood, learning and memory. Structural and functional changes in this vital brain area may thus contribute to impairments associated with depression.

The hippocampus receives abundant cholinergic innervation from the diagonal band and septum (Houser et al., 1983; Gaykema et al., 1990; Semba and Fibiger, 1992; van der Zee and Luiten, 1999). The decreased cholinergic input may account for diminished hippocampal functioning and increase its vulnerability to stress (Craig et al., 2008). Lesion of cholinergic neurons projecting to the hippocampus are known to suppress adult neurogenesis (Cooper-Kuhn et al., 2004; Van der Borght et al., 2005c) and concurrently impair spatial memory in rats (Mohapel et al., 2005). Acetylcholine thus appears crucial for regulating hippocampal neurogenesis (Bruehl-Jungerman et al., 2010). Transgenic mice expressing an inactive form of AChE, and hence expected to have elevated acetylcholine levels, show increased cell proliferation in the dentate gyrus (Cohen et al., 2008). Likewise, pharmacological inhibition of AChE also enhances hippocampal neurogenesis (Mohapel et al., 2005; Kotani et al., 2006). The AChE inhibitor, donepezil, widely used to enhance cognitive function in Alzheimer's disease, has even been shown to reverse chronic stress-induced decrease in survival of the newly-born hippocampal neurons (Kaneko et al., 2006).

Adult hippocampal neurogenesis is hypothesized to be relevant in the pathophysiology and treatment of major depression (Jacobs et al., 2000; Duman, 2004b). In animal models, rodents often display decreased hippocampal neurogenesis (Gould and Tanapat, 1999; Mirescu and Gould, 2006; Krishnan and Nestler, 2008). Such reductions in the generation of new neurons are reversible by antidepressants, comprising in part their mood-improving actions (Santarelli et al., 2003). However, artificially disrupted hippocampal neurogenesis in laboratory animals has not led to the depressive phenotype (Sapolsky, 2004; Eisch et al., 2008). Also, subsequent research has failed to uniformly confirm that the mood-alleviating effects of anti-

depressants depend on hippocampal neurogenesis (Bessa et al., 2009). Although disruption of the neurogenesis process does not fully explain the etiology of depression, yet it may account partly for the associated cognitive impairments as altered cholinergic transmission can reduce neurogenesis and subsequently induce learning and memory deficits. Changes in hippocampal neurogenesis are thus thought to contribute to the hippocampal aspects of major depression. The hippocampus plays a major role in declarative (explicit) memory function (Scoville and Milner, 2000; Burgess et al., 2002; Squire et al., 2004). People who suffer from major depression exhibit memory deficits that are characteristic of hippocampal damage (Sheline et al., 1999; Becker and Wojtowicz, 2007). In a subset of depressed subjects, reduced hippocampal volumes have also been related to functional consequences, such as depression-specific neurocognitive deficits (Sheline et al., 1996; Sheline et al., 1999; Brown et al., 2004). Reduced hippocampal neurogenesis has been suggested as a final common pathway in many brain disorders associated with mood (Duman, 2004b) and cognitive dysfunction, such as geriatric depression and the depression-mild cognitive impairment (MCI)-dementia complex (Maes, 2009). Since acetylcholine regulates neurogenesis, changes in new neuron production may follow the more global changes in the cholinergic system. Depression-associated cognitive and memory deficits may thus represent potential clinical correlates of impaired cholinergic transmission and altered hippocampal neurogenesis (Manji et al., 2001; Becker and Wojtowicz, 2007).

A major predisposing factor to depression, chronic stress, induces damage to hippocampal structure and function in animal models (Duman et al., 1999; McEwen, 2000a; Sapolsky, 2000). Besides affecting the cholinergic system, it decreases hippocampal neurogenesis, and impairs hippocampal-dependant learning and memory (Gould et al., 1999a; Sapolsky, 2003; Mirescu and Gould, 2006). Accumulating evidence supports a relationship between hippocampal neurogenesis and various types of learning and memory (Leuner et al., 2006). It remains unknown, however, whether hippocampal neurogenesis is causally implicated in memory function (Gould et al., 1999a; Feng et al., 2001; Shors et al., 2002; Van der Borght et al., 2005b; Van der Borght et al., 2005a). It seems unlikely that changes in hippocampal neuron production would have an immediate effect on processes underlying learning since the newly-born cells require time to differentiate into functional neurons and become integrated into the pre-existing circuitry (Carlen et al., 2002; Leuner et al., 2006). Therefore, although stress may diminish hippocampal cell proliferation, it may not necessarily induce acute learning deficits on hippocampus-dependent tasks (Akirav et al., 2004). It has been suggested that hippocampal neurogenesis underlies remote, rather than recent, memory formation, although contradicting evidence exists (Feng et al., 2001; Kitamura et al., 2009).

Alternatively, adult dentate neurogenesis has been proposed to play a role in periodic clearance of outdated hippocampal memory traces (Feng et al., 2001; Van der Borgh et al., 2007). This notion has been supported by a recent study demonstrating that suppressed neurogenesis in rodents is accompanied by a prolonged hippocampus-dependent period of associative fear memory (Kitamura et al., 2009). Reduced neurogenesis might thus hinder erasure of the hippocampal memory trace and its transfer to the neocortex. Such impaired clearance of old disused memories from the hippocampus could in turn compromise its learning capacity and affect the formation of long-term memory. In view of the above, presumed chronic impairment of hippocampal neurogenesis in depression may at least partly account for development of hippocampal dysfunction leading to cognitive and mnemonic deficits.

Taken together, alterations in the central cholinergic system could affect adult neurogenesis and hippocampal function, giving way to depression-associated memory deficits. However, besides the explicit memory dysfunction, depressed patients often show a more widespread impairment in cognitive function, deficits in attention and working memory (Austin et al., 2001; Porter et al., 2003; Clark et al., 2009), suggesting that dysfunctions are not focally localized to the hippocampus, but may be present more globally.

Involvement of the cholinergic system in depression: beyond the hippocampus

Although major depressive disorder is associated with functional impairment of multiple brain regions, the hippocampus has been the preferred region of investigation. Such bias may have occurred due to the discovery of hippocampal neurogenesis and its linkage to depression, as well as due to the fact that hippocampus is highly enriched with glucocorticoid receptors and is severely affected by stress. Nevertheless, the structural and functional changes associated with depression point to the involvement of several other brain regions in addition (Sheline, 2003). Here, we limit our discussion to a selected few. First, we will address the potential role of the cholinergic system in depression-associated changes in the prefrontal cortex and amygdala. Then, we will briefly discuss the cholinergic input to the SCN, the regulator of circadian rhythms shown to be often disturbed in depression.

Importantly, both the prefrontal cortex and amygdala receive vast cholinergic input, suggesting a vital role for acetylcholine in the modulation of their function

(Houser et al., 1983; Woolf, 1991; Semba and Fibiger, 1992). Moreover, cognitive symptoms accompanying depression often reflect dysfunctions in these limbic structures (Clark et al., 2009). For instance, depressed individuals show deficits in executive function, such as impaired performance in tests of attention and working memory, which relate to structural abnormalities often observed in the prefrontal cortex during depression (Rogers et al., 2004). Different subregions of the prefrontal cortex are suggested to contribute to diverse symptoms of depression, and their role has been previously reviewed (Koenigs and Grafman, 2009). Postmortem analysis suggests a causal role for altered muscarinic receptor expression, particularly in the dorsolateral prefrontal cortex of depressed subjects (Gibbons et al., 2009). Potential cholinergic involvement of the prefrontal cortex in the cognitive dysfunctions of affective disorders is further substantiated by a preclinical study reporting cognitive deficits in mice lacking M2 muscarinic receptors (Seeger et al., 2004).

Cognitive dysfunction in depression is also characterized by a negativity bias – an enhanced responsiveness to, and memory for, emotionally negative stimuli, attributed to the impaired functioning of both the prefrontal cortex and the amygdala complex (Fales et al., 2008). Mental rumination is a frequent symptom of depression, and may depend on hyperactivity of the amygdala leading to enhancement of negative thoughts and memories. Increased activity of the amygdala has been demonstrated in depressed patients, and is thought to parallel the suppressed activity of the dorsolateral prefrontal cortex and dampened hippocampal function (Sheline et al., 2001; McDonald et al., 2004; Fales et al., 2008). Among the heterogeneous nuclei of amygdala, the basolateral amygdala (BLA) is especially important since it serves as an interface between the sensory and cognitive realms (Davis et al., 1994; LeDoux, 2003). Notably, the BLA is critically involved in the modulation of memory consolidation, which is achieved through influences from cholinergic, noradrenergic and other brain systems (McGaugh, 2004). The BLA is abundantly innervated by cholinergic neurons, originating mainly from the nucleus basalis of the forebrain (Woolf and Butcher, 1982; Houser et al., 1983; Semba and Fibiger, 1992; Roozendaal et al., 1997; van der Zee et al., 1997). In laboratory animals, experimental suppression of this cholinergic transmission by lesion of the nucleus basalis or intra-amygdalar infusion of muscarinic antagonists impairs memory for various learning tasks. Conversely, intra-BLA infusion of muscarinic agonists or AChE inhibitors enhances memory or attenuates its impairment (Vazdarjanova and McGaugh, 1999; Power and McGaugh, 2002; Schroeder and Packard, 2002). These findings suggest that cholinergic activity is essential for amygdalar modulation of memory consolidation (McGaugh et al., 2002; Power et al., 2003). Glucocorticoids also play a role in the consolidation of learning experiences, and the BLA is critically involved in their memory-modulating effects (McGaugh,

2000; Roozendaal, 2000; McGaugh and Roozendaal, 2002). Glucocorticoids as well as stress have been shown to change structure and function of the BLA, resulting in hypertrophy and increased excitability (Rainnie et al., 2004; de Quervain et al., 2009). Associated impairments in working memory are attributed to the interaction of the hyperactive BLA with the medial prefrontal cortex (Roozendaal et al., 2004; de Quervain et al., 2009). The functional consequences of increased amygdala influence on thoughts and emotions are however not possible to adequately assess in preclinical research models. Yet, the stress and depression-associated prefrontal cortical and amygdalar dysfunctions may be due, at least in part, to altered activity of the cholinergic system, given its strong projections to these areas.

The SCN, situated in the anterior hypothalamus, receives direct cholinergic input from the nucleus basalis of the forebrain and is responsible for controlling circadian rhythms (Bina et al., 1993; Tuma et al., 2005; Castillo-Ruiz and Nunez, 2007). Clinical findings suggest that many diverse rhythms can be disrupted in depression, including the 24-hour profiles of various hormones, neurotransmitters, body temperature as well as sleep architecture and timing (Turek, 2007; Lam, 2008). Given the cholinergic input to the SCN, such depression-associated disturbances of internal rhythms and sleep-wake cycle may at least partly arise from changes in the cholinergic system. In fact, impaired cholinergic transmission has recently been linked to disruptions in melatonin production, sleep-wake cycle and other circadian rhythms in Alzheimer's disease (Klaffke and Staedt, 2006). Cholinergic regulation of the SCN has also been implicated in cognitive processes (Van der Zee et al., 2004). As depression often accompanies or even precedes the Alzheimer's disease, similar changes may underlie both pathologies (Starkstein et al., 2008). Recognition that desynchronization of circadian rhythms also plays an important role in depression has led to the development of the first melatonergic antidepressant, agomelatine (Tuma et al., 2005; Lam, 2008; Popoli, 2009). Besides being a potent agonist of the melatonergic (MT₁/MT₂) receptors, agomelatine also acts as an antagonist of the serotonergic (5-HT_{2C}) receptors (Audinot et al., 2003; Millan et al., 2003). This novel drug combines antidepressant efficacy with beneficial effect on sleep quality, achieved via synergy between the melatonergic and 5-HT_{2C} receptors, highly expressed in the SCN and limbic brain areas (Popoli, 2009). Preclinical studies have already demonstrated a variety of agomelatine-mediated changes on neural plasticity (Banasr et al., 2006; Conboy et al., 2009; Soumier et al., 2009), including its beneficial action in the stress-compromised brain (Dagyte et al., 2010d). However, the effects of agomelatine on the cholinergic transmission are not yet known and await future investigation.

CONCLUSION AND FUTURE DIRECTIONS

Dysfunctions in the cholinergic system alone do not fully explain the etio-pathophysiology of major depressive disorder, but they represent likely contributors to its wide spectra of associated symptoms, particularly those involving cognition. Acetylcholine plays an important role in regulation of hippocampal neurogenesis, believed to be involved in the pathophysiology and treatment of depressive disorder. Alterations in the central cholinergic system may thus affect adult neurogenesis and hippocampal function, leading in turn to the cognitive deficits observed in depression. Besides the hippocampus, cholinergic neurons from the basal forebrain also project to other brain structures implicated in depressive disorder. Therefore, cholinergic changes may also account for depression-associated circadian rhythm desynchronization as well as cognitive symptoms related to the functions of such structures as the prefrontal cortex and amygdala. Future research is needed to elucidate more precise cholinergic changes that underlie depression, but as cholinergic drugs continue to modify cognitive deficits characteristic of this disorder, application of these neuropharmacological findings may provide a new therapeutic niche while yielding valuable insight into the pathophysiology of this complex illness.

In conclusion, the cholinergic system plays a considerable, albeit poorly recognized, role in major depression-associated cognitive dysfunctions (see figure 6.1). Yet, the cholinergic system represents merely one of many players involved in this severe illness. The complex interaction of multiple factors and neurobiological systems is thought to underlie the intricate changes associated with depressive disorder, in a variety of brain areas. Future research can thus greatly benefit from an integrated approach in attempts to elucidate the interaction among diverse factors of depression, rather than focusing on changes of one neurobiological system. Such cohesive knowledge might not only shed light on the more poorly understood aspects of this disorder but also pave the way to development of novel multifaceted therapies against it.

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